

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

A15



⑪ Publication number: **0 435 362 B1**

⑫ **EUROPEAN PATENT SPECIFICATION**

④⑤ Date of publication of patent specification :
21.04.93 Bulletin 93/16

⑤① Int. Cl.⁵: **A61K 31/65, // (A61K31/65, 31:60), (A61K31/65, 31:19)**

②① Application number : **90203190.5**

②② Date of filing : **03.12.90**

⑤④ Composition comprising non-steroidal anti-inflammatory agent and effectively non-antibacterial tetracycline.

③⑥ Priority : **04.12.89 US 445410**

④③ Date of publication of application :
03.07.91 Bulletin 91/27

④⑤ Publication of the grant of the patent :
21.04.93 Bulletin 93/16

⑧④ Designated Contracting States :
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

⑤⑥ References cited :
EP-A- 0 195 906
US-A- 4 666 897

⑦③ Proprietor : **THE RESEARCH FOUNDATION OF STATE UNIVERSITY OF NEW YORK**
PO Box 9
Albany, New York 12201-0009 (US)

⑦② Inventor : **Golub, Lorne M.**
29 Whitney Gate
Smithtown, New York 11787 (US)
Inventor : **McNamara, Thomas F.**
P.O. Box 44
Port Jefferson, New York 11777 (US)
Inventor : **Ramamurthy, Nangavarum S.**
10 Lynam Court
Smithtown, New York 11787 (US)
Inventor : **Greenwald, Robert A.**
5 Vaux Hall Court
Melville, New York 11747 (US)

⑦④ Representative : **Smulders, Theodorus A.H.J.,**
Ir. et al
Vereenigde Octrooibureaux Nieuwe Parkdaan
97
NL-2587 BN 's-Gravenhage (NL)

Note : Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent grant d. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid (Art. 99(1) European patent convention).

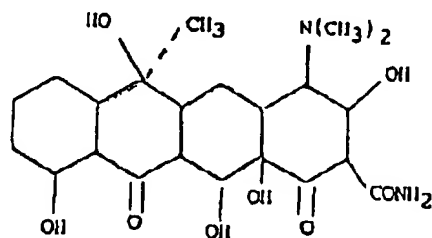
EP 0 435 362 B1

Description

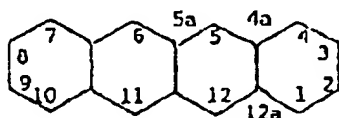
The present invention relates to an anti-collagenolytic composition useful in the treatment of rheumatoid arthritis and other tissue-destructive conditions associated with excess collagenolytic activity.

Background of the Invention

Tetracyclines constitute a family of well known natural and synthetic broad spectrum antibiotics. The parent compound, tetracycline, exhibits the following general structure:



The numbering system of the ring nucleus is as follows:



Tetracycline as well as the 5-OH (tetracycline) and 7-C1 (Aureomycin) derivatives exist in nature, and are well known antibiotics. Natural tetracyclines may be modified without losing their antibiotic properties, although certain elements of the structure must be retained. The modifications that may and may not be made to the basic tetracycline structure have been reviewed by Mitscher in *The Chemistry of Tetracyclines*, Chapter 6. According to Mitscher, the substituents at positions 5-9 of the tetracycline ring system may be modified without the complete loss of antibiotic properties. Changes to the basic ring system or replacement of the substituents at positions 1-4 and 10-12, however, generally lead to synthetic tetracyclines with substantially less or effectively no antibacterial activity. For example, 4-dedimethylamino-tetracycline is commonly considered to be a non-antibacterial tetracycline.

The use of tetracycline antibiotics, while effective, may lead to undesirable side effects. For example, the long term administration of antibiotic tetracyclines may reduce or eliminate healthy flora, such as intestinal flora, and may lead to the production of antibiotic resistant organisms or the overgrowth of yeast and fungi.

In addition to their antibiotic properties, tetracyclines are also known to inhibit the activity of collagen destructive enzymes such as mammalian collagenase, macrophage elastase and bacterial collagenase; Golub et al., *J. Periodont. Res.* 20, 12-23 (1985) and Golub, et al., *J. Periodont. Res.* 1989, submitted for publication. Collagen is a major component of connective tissue matrices such as those in bone, synovium, eye, skin, tendons and gingiva. Collagenase, which is naturally produced by only a few types of bacteria and in a number of tissues and cells in mammals, degrades collagen.

The degradation of collagen by mammalian collagenase is a natural part of the normal growth-degradation-regeneration process that occurs in connective tissue. The production of collagenase, however, may become excessive. Such excessive collagenase production often results in the pathologic and debilitating destruction of connective tissue.

U.S. Patent No. 4,704,383 to McNamara et al. discloses that tetracyclines having substantially no effective antibacterial activity inhibit collagenolytic enzyme activity in rats. McNamara et al. also report that non-antibacterial tetracyclines reduce bone resorption in organ culture, although no clinical studies were reported.

Earlier, U.S. Patent No. 4,666,897 to Golub, et al. disclosed that tetracyclines in general, including commercially-available antimicrobial forms of the drug, inhibit excessive bone resorption.

There have been a number of suggestions that tetracyclines, including non-antibacterial tetracyclines, are effective in treating arthritis in rats. See, for example, Golub et al., "Tetracyclines (TCs) Inhibit Metalloproteinases (MPs): *In Vivo* Effects In Arthritic And Diabetic Rats, And New *In Vitro* Studies," abstract presented at

Matrix Metalloproteinase Conference, Destin, Florida, September 11-15, 1989; Breedveld, "Suppression Of Collagen And Adjuvant Arthritis By A Tetracycline," Northeastern Regional Meeting Of The Amer. Rheum. Assoc., Atlantic City, New Jersey, October 23-24, 1987. For related commentary regarding the effect of non-antibacterial tetracyclines on bone loss see Sipos et al., "The Effect Of Collagenase Inhibitors On Alveolar Bone Loss Due To Periodontal Disease In D Salivated Rats," abstract presented at Matrix Metalloproteinase Conference, Destin, Florida, September 11-15, 1989.

An effect of tetracyclines independent of antibiotic effects has, however, not been established for human patients with rheumatoid arthritis. Thus, Skinner et al., Arthritis and Rheumatism 14, 727-732 (1971), reported no significant benefit from tetracycline therapy for human sufferers of rheumatoid arthritis even though Greenwald et al., reported in J. Rheumatol. 14: 28-32 (1987) that the oral administration of a tetracycline to humans with severe rheumatoid arthritis decreased the collagenase activity in the joint tissues.

It is known that, unlike tetracyclines, non-steroidal anti-inflammatory agents are useful in the symptomatic treatment of rheumatoid arthritis as well as other inflammatory diseases. Such agents, however, do not effectively prevent long term destruction of joint-connective tissues including tendons, cartilage and bone caused by the presence of excessive amounts of collagenase.

Excessive collagenase activity has also been implicated in certain skin disorders. According to White, Lancet, April 29th, 1989, p. 966 (1989) the tetracycline minocycline is effective in treating dystrophic epidermolysis bullosa, which is a life-threatening skin condition believed to be related to excess collagenase.

The effectiveness of tetracycline in skin disorders has also been studied by Elewski et al., Journal of the American Academy of Dermatology 8, 807-812 (1983). Elewski et al. disclosed that tetracycline antibiotics may have anti-inflammatory activity in skin and speculate that a portion of the therapeutic effect in skin diseases associated with bacteria, e.g., acne, may be due to inhibition of bacterially induced inflammation rather than a direct anti-bacterial effect.

Similarly, Plewig et al., Journal of Investigative Dermatology 65, 532-532 (1975), disclose experiments designed to test the hypothesis that anti-microbials are effective in treating inflammatory dermatoses. The experiments of Plewig et al. establish that tetracyclines have anti-inflammatory properties in treating pustules induced by potassium iodide patches.

There has also been speculation that collagenase is involved in bone resorption. For example, Cowen et al., Biochemistry International 11, 273-280 (1985), hypothesize that osteoblast production of collagenase might be an initiating event in bone resorption, leaving minerals to be phagocytosed by osteoclasts.

Further, Dellaissé et al., Biochemical and Biophysical Research Communications 133, 483-490 (1985), propose that collagenase plays a critical role in bone resorption. The work of Dellaissé et al., shows that inhibition of mammalian collagenase and related tissue metallo-proteinases prevent the degradation of bone collagen, thus inhibiting the resorption of explanted mouse bones in tissue culture.

The use of tetracyclines in combination with non-steroidal anti-inflammatory agents has been studied in the treatment of inflammatory skin disorders caused by acne vulgaris. Wong et al., Journal of American Academy of Dermatology 11, 1076-1081 (1984), studied the combination of tetracycline and ibuprofen and found that tetracycline was an effective agent against acne vulgaris while ibuprofen was useful in reducing the resulting inflammation by inhibition of cyclooxygenase. Funt, Journal of the American Academy of Dermatology 13, 524-525 (1985), disclosed similar results by combining the tetracycline minocycline and ibuprofen.

In most of the above studies, the tetracycline was believed to be useful for its antibiotic effect. Therefore, with the exception of the disclosure in the McNamara et al. patent, antibacterial tetracyclines were used despite their undesirable side effects.

Despite the above studies, an effective long term treatment for rheumatoid arthritis and other tissue-destructive conditions associated with excess collagenolytic activity has remained elusive. It is an object of this invention to provide such a treatment. Another object of this invention is to provide such a treatment while avoiding the side effects of antibacterial tetracycline therapies.

SUMMARY OF THE INVENTION

It has now been discovered that these and other objectives can be achieved by providing a pharmaceutical composition for treating mammals suffering from rheumatoid arthritis and other tissue-destructive conditions associated with excess metalloproteinase activity comprising (a) an amount of a tetracycline that is effectively anti-collagenase but that is not effectively anti-microbial; and (b) an amount of a non-steroidal anti-inflammatory agent which, when combined with the effectively anti-collagenase amount of tetracycline, results in a significant reduction of bone loss. The amount of tetracycline used in the present invention is that which is effectively non-antibacterial in the patient. Thus, tetracyclines generally used for anti-bacterial properties can also be used herein in reduced amounts which are effectively non-antibacterial.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 dramatically depicts the unexpectedly excellent inflammation treatment characteristics achieved by use of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to the treatment of tissue-destructive conditions associated with excess activity of matrix-degrading proteinases such as the metalloproteinases. Typical metalloproteinases include, for example, collagenase and gelatinase. Tissue-destructive conditions treated in accordance with the present invention include rheumatoid arthritis, osteoarthritis, corneal ulceration, epidermolysis, bullosa, metabolic bone diseases including osteoporosis, disorders involving damage to basement membranes such as diabetic renal disease, disorders involving cellular passage through basement membranes such as metastatic cancer, and periodontal diseases.

The conditions treated by the present invention occur in mammals. Mammals include human beings and laboratory animals such as mice and rats.

Reports that chemically modified non-antimicrobial tetracycline analogs inhibit metalloproteinases *in vivo* in rats; that chemically modified tetracyclines reduced alveolar bone loss associated with periodontal disease in desalivated rats; that antimicrobial and non-antimicrobial tetracyclines inhibit bone resorption in tissue culture; that the tetracycline minocycline reduced the incidence and severity of arthritis in rats; and that antibacterial tetracyclines reduce bone resorption *in vivo* (Golub et al., U.S. Patent 4,666,897) suggest that administration of non-antimicrobial doses of tetracyclines are expected to reduce bone loss in arthritic animals. The present inventors have unexpectedly found, however, that this is not the case. When arthritic rats were treated with non-antimicrobial doses of the chemically modified tetracycline 4-dedimethylaminotetracycline, there was no significant reduction in bone loss.

Also unexpectedly, the present inventors have found that bone loss is significantly reduced when mammals suffering from arthritis are treated with an amount of a tetracycline that is effectively anti-metalloproteinase but that is not effectively antimicrobial in combination with a non-steroidal anti-inflammatory agent. Bone loss may be reduced either by the prevention of bone resorption or stimulation of new bone formation.

The tetracycline may be any tetracycline administered to a mammal in a dose that is effectively non-antimicrobial in the mammal. Preferably, the tetracycline is modified so as to reduce its antimicrobial properties. Methods for reducing the anti-microbial properties of a tetracycline were disclosed in "The Chemistry of the Tetracyclines", Chapter 6, Mitscher, Ed. at page 211. As pointed out by Mitscher, modification at positions 1, 2, 3, 4, 10 and 12a lead to loss of bioactivity. The use of such modified tetracyclines is preferred in the present invention, since they can be used at higher levels than anti-microbial tetracyclines with fewer side effects.

The preferred tetracyclines are those that lack the dimethylamino group at position 4. Such chemically modified tetracyclines include, for example, 4-dedimethylaminotetracycline, 4-dedimethylamino-5-oxytetracycline, 4-dedimethylamino-7-chlorotetracycline, 4-hydroxy-4-dedimethylaminotetracycline, 5a, 6-anhydro-4-hydroxy-4-dedimethylaminotetracycline, 6-demethyl-6-deoxy-4-de-dimethylaminotetracycline, and 6- α -deoxy-5-hydroxy-4-de-dimethylaminotetracycline.

Also tetracyclines altered at the 2 carbon position to produce a nitrile, e.g., tetracyclinoitrile are useful as non-antimicrobial anti-metalloproteinase agents.

Further examples of tetracyclines modified for reduced anti-microbial activity include 6- α -benzylthiomethylenetetracycline, the 2-nitrilo analog of tetracycline, the mono-N-alkylated amide of tetracycline, 6-fluoro-6-demethyltetracycline, or 11 α -chlorotetracycline.

The amount of tetracycline is an amount that is effectively anti-collagenase while not effectively antimicrobial. An amount of a tetracycline is effectively anti-collagenase if it significantly reduces anti-collagenase activity. A tetracycline is not effectively anti-microbial if it does not significantly prevent the growth of microbes. The maximal dosage for humans is the highest dosage that does not cause side effects. For the purpose of the present invention, side effects include clinically significant anti-microbial activity, as well as toxic effects. For example, a dose in excess of 50 mg/kg/day would likely produce side effects in most mammals, including humans.

The non-steroidal anti-inflammatory agent may be selected from the various classes of such compounds. Such classes include, salicylates such as acetylsalicylic acid and diflunisal; acetic acids such as indomethacin, sulindac, tolmetin, diclofenac, and etodolac; propionic acids such as flurbiprofen, naproxen, and ketoprofen; fenamates such as meclofenamate; and oxicams such as piroxicam.

The preferred non-steroidal anti-inflammatory agents include flurbiprofen, piroxicam, tolmetin sodium, ibu-

profen, naproxen and indomethacin.

The amount of the non-steroidal anti-inflammatory agent is an amount which, when combined with the effectively anti-collagenase amount of tetracycline, results in a significant reduction of bone loss in mammals suffering from tissue-destructive conditions associated with excess metalloproteinase activity. The amount depends on the particular anti-inflammatory agent used, the mammal to which the composition is administered, and the amount of the tetracycline in the composition. Some typical doses for routine human use include, 20 mg/day for piroxicam, 150 mg/day for indomethacin, 1600-1800 mg/day for tolmetin, 1000 mg/day for naproxen, and 3200 mg/day for ibuprofen.

A suitable amount of 4-dedimethylamino tetracycline is 15 mg/kg. A suitable amount of anti-inflammatory agent in combination with 30 mg/kg 4-dedimethylamino tetracycline would be 1-8 mg/kg flurbiprofen, 0.3 mg/kg piroxicam and 40 mg/kg ibuprofen.

As a guideline for providing the proper amount of anti-inflammatory agents for implementing the present invention, a rule of thumb is to administer an amount which is 20% to 80% of the conventional anti-inflammatory dose for treating arthritis. Thus, the dosage could be from as small as 10 mg/person/day for piroxicam, to as great as 3200 mg/person/day for ibuprofen. In any event, the practitioner is guided by skill and knowledge in the field and the present invention includes dosages which are effective to achieve the described phenomenon.

The preferred pharmaceutical composition for use in the present invention comprises a combination of the tetracycline and the anti-inflammatory agent in a suitable pharmaceutical carrier. The means of delivery of the pharmaceutical carrier with active may be in the form of a capsule, compressed tablet, pill, solution or suspension suitable for oral administration to a mammal. Other means of delivery include a gel for topical application for corneal ulcers, periodontal disease, etc. It is contemplated that carriers be included which are suitable for administration orally, topically, by injection into a joint, and by other selected means.

25 **EXAMPLES OF THE INVENTION**

EXAMPLE I

The following experiment was carried out to determine the effect of a non-steroidal anti-inflammatory drug (flurbiprofen), a chemically modified non-antimicrobial tetracycline (4-dedimethylaminotetracycline; CMT), and a flurbiprofen/CMT combination on: (i) the collagenase and gelatinase activities, (ii) the severity of inflammation assessed clinically, and (iii) the loss of bone assessed by radiographs in the tissues and joints of rats with experimental arthritis.

Thirty-six adult Lewis rats were made arthritic by injection of Freund's adjuvant and the animals distributed into the following experimental groups: **Group I** - untreated arthritic rats; **Group II** - arthritic rats administered flurbiprofen daily by oral gavage (1.0 mg per rat); **Group III** - arthritic rats administered CMT daily by oral gavage (3 mg per rat); **Group IV** - arthritic rats administered both drugs. After a 2-3 week experimental period (2 weeks for the 6 rats/group assessed for enzyme activity; 3 weeks for the 3 rats/group assessed for enzyme activity; 3 weeks for the 3 rats/group assessed by x-rays for bone loss), the rats were killed, the hind paws obtained, the skin removed and the inflamed subcutaneous tissues overlying the arthritic joints were dissected (all dissection and extraction procedures at 4°C). The tissues were minced, weighed, extracted, and the extracts partially purified by ammonium sulfate precipitation using techniques described previously (Ramamurthy and Golub, *J. Periodontal Res.* 17, 455, (1983)). The extracts of the diseased tissue were then concentrated 5-fold and aliquots were incubated (a) with [³H-methyl] gelatin (denatured type I rat skin collagen) at 37°C for 4 hours to measure gelatinase activity. The undigested gelatin was precipitated with trichloroacetic acid and, after centrifugation, aliquots of the degradation products in the supernatants were measured in a liquid scintillation spectrometer; (b) for the collagenase assay, the extracts were incubated with [³H-methyl] collagen for 18 hours at 22°C and the radiolabeled collagen components (α chains) and degradation fragments (β^A) were assessed by a combination of SDS-polyacrylamide gel electrophoresis & fluorography as described previously (Golub et al. *J. Periodontal Res.* 20, 12 (1985)).

Results:

1. The untreated arthritic rats showed the highest level of tissue-destructive metalloproteinase activity (gelatinolytic and collagenolytic) which was associated with the most inflammatory swelling of the paws and the most bone loss in the joints, the latter assessed by x-rays.
2. The arthritic rats treated with flurbiprofen alone showed a reduction in swelling of the paws, a slight reduction in metalloproteinase activity (although the reduction in gelatinolytic activity was not statistically

significant;

Note - collagenolytic activity assessed by fluorography was not analyzed statistically, and slight reduction of bone loss in the joints.

3. The arthritic rats treated with CMT alone showed a significant reduction in metalloproteinase activity, a slight reduction in joint bone loss, and no detectable anti-inflammatory effect (no detectable reduction in paw swelling).

4. The arthritic rats treated with CMT plus flurbiprofen showed complete inhibition of collagenolytic and the greatest reduction of gelatinolytic activity; the greatest reduction of bone loss in the joints; and a reduction in paw swelling as great or greater than observed with flurbiprofen alone.

TABLE I

THE EFFECT OF FLURBIPROFEN OR CMT ALONE,
OR THE TWO COMBINED, ON GELATINOLYTIC ACTIVITY
IN INFLAMED ARTHRITIC RAT PAW TISSUE*

<u>Experimental Group</u>	<u>\pm[³H-Methyl] Gelatin Degraded</u>	<u>Statistical Significance vs. Group I</u>
I. (Untreated Arthritics)	76.2 \pm 1.4	_____
II. (Arthritics + Flurbiprofen)	68.3 \pm 3.2	Not significant; p>0.05
III. (Arthritics + CMT)	52.2 \pm 4.9	Significant; p<0.01
IV. (Arthritics + Both Drugs)	45.6 \pm 3.4	Significant; p<0.01

* Each value represents the mean \pm S.E.M. for 6 rats/group.

From the above results, one can conclude that the treatment of arthritic rats with CMT alone or with flurbiprofen alone each produced some amelioration of the pathologic joint changes. However, treatment of the arthritis with the two drugs combined produced the greatest reduction of the tissue-destructive inflammatory joint changes.

EXAMPLE II

Yet a further experiment was conducted to determine the efficacy of the invention by comparing results achieved using chemically modified non-antibacterial tetracycline (4-de-dimethylaminotetracycline) alone, the non-steroidal anti-inflammatory drug flurbiprofen, and a combination of flurbiprofen and CMT on arthritically-induced bone and joint destruction. In order to conduct the experiment, the investigators used adult Lewis rats having a starting body weight of about 120 grams each. The rats were distributed into five groups which included one six-rat control group which was not injected to induce arthritis, and forty-eight adult Lewis rats which

were made arthritic by injection of Freund's adjuvant. The arthritic rats were distributed into the following experimental groups: **Group I** - untreated arthritic rats were orally administered vehicle alone, i.e., 2% carboxymethylcellulose; **Group II** - arthritic rats treated on a daily basis by oral intubation with the chemically modified tetracycline (CMT) at a dosage rate of 4 mg/day per rat; **Group III** - arthritic rats treated daily by oral intubation with the non-steroidal anti-inflammatory drug flurbiprofen (at a rate of 0.5 mg/day per rat); **Group IV** - arthritic rats treated with a combination of CMT plus the flurbiprofen in the doses previously described with respect to treatment with the single active ingredient.

Twenty-three days after inducing arthritis, half of the rats in each group were sacrificed. The hind paws were dissected and radiographs of the bones and joints were taken using high-sensitivity x-ray film. The x-rays were scored, in a blinded fashion, by two independent experienced examiners, to assess the severity of arthritic bone destruction in the five different groups of rats. The scores were given in accordance with the following scale: 1=normal, 2=mild, 3=moderate, and 4=severe bone destruction. An additional experienced examiner scored the results after the initial examination. The results have been set forth in Table II.

TABLE II

Experimental Group	Bone Destruction Score	Serum concentration of CMT ($\mu\text{g/ml}$) *
Non-arthritic controls	1.0	0 ± 0
Arthritics + vehicle	2.8	0 ± 0
Arthritics + CMT	2.4	12.8 ± 0.5 (SEM)
Arthritics + flurbiprofen	2.0	0 ± 0
Arthritics + combination	1.1	12.4 ± 1.3 (SEM)

* The serum data was obtained from rats sacrificed on day 14.

The data above represents the average score for the three examiners for six bones per group, except that five bones were used for the group treated with the combination of CMT and NSAID.

Results:

- Each of the active ingredients, CMT and the flurbiprofen used alone had only slight inhibitory effects on the arthritically induced bone and joint destruction during the twenty-three day protocol. This result is quite surprising in view of the earlier beliefs, as set forth in the literature, which led the investigators to expect that each of the ingredients might separately be effective.
- The combination of CMT and flurbiprofen exhibited an inordinately potent ability to prevent bone and joint destruction in rats which had been arthritically induced during the experiment.
- Further information gathered from the results of this experiment show that the oral administration of flurbiprofen in combination with CMT did not reduce the blood level of CMT.

Further data was gathered by making physical measurements of the paw diameters before and during the protocol to determine the degree of inflammation. The results shown in Fig. 1 clearly depict a dramatic reduction in the inflammation as a result of the combined use CMT and flurbiprofen.

In fact, the combination of CMT and flurbiprofen administered to arthritic rats produced paw diameter scores essentially identical to the scores obtained from the normal non-arthritic rats. The paws taken from the rats treated with CMT alone show high inflammation. Paws taken from rats subjected to flurbiprofen treat-

ment alone, on the other hand, produced a distinct anti-inflammatory effect, as expected. The untreated paws from the arthritic rats displayed expected normal inflammatory paw diameter measurements. This is a dramatic showing of the efficacy of the combined actives.

Basically, the results of the second experiment confirm the results of the first experiment, and also dramatize the potential effectiveness of the present invention in treatment of tissue-destructive conditions.

Claims

1. A composition for treating mammals suffering from rheumatoid arthritis and other tissue-destructive conditions associated with excess metalloproteinase activity comprising;
 - (a) an amount of a tetracycline that is effectively anti-collagenase but which is not effectively antimicrobial; and
 - (b) an amount of a non-steroidal anti-inflammatory agent which, when combined with the effectively anti-collagenase amount of tetracycline, results in a significant reduction of bone loss.
2. A composition according to claim 1 wherein the tetracycline is a dedimethylaminotetracycline.
3. A composition according to claim 2 wherein the dedimethylaminotetracycline is 4-de(dimethylamino)-tetracycline, 4-de(dimethylamino)-5-oxytetracycline, 4-de(dimethylamino)-7-chlorotetracycline, 6-deoxy-6-demethyl-4-dedimethylamino-tetracycline, and 6- α -deoxy-5-hydroxy-4-dedimethylamino-tetracycline.
4. A composition according to claim 3 wherein the tetracycline is 6 α -benzylthiomethylenetetracycline, the 2-nitrilo analog of tetracycline, the mono-N-alkylated amide of tetracycline, 6-fluoro-6-demethyltetracycline, or 11 α -chlorotetracycline.
5. A composition according to claim 1 wherein the non-steroidal anti-inflammatory agent is selected from salicylates, acetic acids, propionic acids, fenamates, pyrazoles, and oxicams.
6. A composition according to claim 5 wherein said salicylate is selected from acetylsalicylic acid and diflunisal, said acetic acid is selected from indomethacin, sulindac, tolmetin, diclofenac and etodolac, and said propionic acid is selected from flurbiprofen, naproxen, ketoprofen, and ibuprofen, said oxicam is selected from piroxicam and isoxicam, and said fenamate is selected from meclofenamate and flufenamic acid.
7. Use of (a) an amount of a tetracycline that is effectively anti-collagenase but which is not effectively antimicrobial, and (b) an amount of a non-steroidal anti-inflammatory agent which, when combined with the effectively anti-collagenase amount of tetracycline, leads to a significant reduction of bone loss, for preparing a pharmaceutical product, which contains (a) and (b) as a combined preparation for simultaneous, separate or sequential use in the treatment of mammals suffering from rheumatoid arthritis and other tissue-destructive conditions associated with excess metalloproteinase activity.

Patentansprüche

1. Zusammensetzung zur Behandlung von Säugetieren, die an rheumatoider Arthritis und anderen gewebsschädigenden Zuständen, die mit übermäßiger Metalloproteinase-Aktivität assoziiert sind, leiden, umfassend:
 - (a) eine anti-Kollagenase-, aber nicht anti-mikrobiell-wirksame Menge eines Tetracyclins und
 - (b) eine Menge eines nicht-steroiden anti-inflammatorischen Agens, das in Verbindung mit der anti-Kollagenase-wirksamen Tetracyclinmenge eine deutliche Herabsetzung des Knochenschwundes bewirkt.
2. Zusammensetzung gemäß Anspruch 1, wobei das Tetracyclin Desdimethylaminotetracyclin ist.
3. Verbindung gemäß Anspruch 2, wobei das Desdimethylaminotetracyclin 4-Des(dimethylamino)-tetracyclin, 4-Des(dimethylamino)-5-oxytetracyclin, 4-Des(dimethylamino)-7-chlortetracyclin, 6-Desoxy-6-desmethyl-4-desdimethylamino-tetracyclin und 6- α -Desoxy-5-hydroxy-4-desdimethylamino-tetracyclin ist.

4. Zusammensetzung gemäß Anspruch 3, wobei das Tetracyclin 6-ä-Benzylthiomethylentetracyclin, das 2-Nitril-Analog des Tetracyclins, das mono-N-alkyliert Amid des Tetracyclins, 6-Fluor-6-desmethyltetracyclin oder 11-ä-Chlortetracyclin ist.
5. Zusammensetzung gemäß Anspruch 1, wobei das nicht-steroidale anti-inflammatorische Agens ausgewählt ist aus den Salicylaten, Acetatsäuren, Propionsäuren, Fenematen, Pyrazolen und Oxicamen.
6. Zusammensetzung gemäß Anspruch 5, wobei die Salicylate ausgewählt sind aus Acetylsalicylsäure und Diflunisal; die Acetatsäure ausgewählt ist aus Indomethacin, Sulindac, Tolmethin, Didofenac und Etodolac; die Propionsäure ausgewählt ist aus Flurbiprofen, Naproxen, Ketoprofen und Ibuprofen; das Oxicam ausgewählt ist aus Piroxicam und Isoxicam; und das Fenamat ausgewählt ist aus Meclofenamat und Flufenamsäure.
7. Verwendung von (a) einer anti-Kollagenase-, aber nicht anti-mikrobiell wirksamen Menge eines Tetracyclins und (b) einer Menge eines nicht-steroiden anti-inflammatorischen Agens, das in Verbindung mit der anti-Kollagenase-wirksamen Menge des Tetracyclins zu einer deutlichen Herabsetzung des Knochen-schwundes führt, zur Zubereitung eines pharmazeutischen Produkts, das (a) und (b) in einer Kombinationszubereitung zur gleichzeitigen, getrennten oder aufeinanderfolgenden Verwendung enthält und zwar zur Behandlung von Säugetieren, die an rheumatoider Arthritis oder anderen gewebsschädigenden Zuständen, die mit einer übermäßigen Metalloproteinase-Aktivität assoziiert sind, leiden.

Revendications

1. Une composition pour le traitement de mammifères souffrant de polyarthrite rhumatoïde et d'autres affections destructrices des tissus associées à une activité excessive de métalloprotéinases, comprenant :
 (a) une quantité de tétracycline qui est effectivement anticollagénase mais qui n'est pas effectivement antimicrobienne ;
 et
 (b) une quantité d'agent non-stéroïde anti-inflammatoire qui, lorsqu'elle est combinée à la quantité effectivement anticollagénase de tétracycline, a pour conséquence une réduction notable de la déperdition osseuse.
2. Une composition selon la revendication 1 où la tétracycline est une dediméthylaminotétracycline.
3. Une composition selon la revendication 2 où la dediméthylaminotétracycline est la 4-de(diméthylamino)-tétracycline, la 4-de(diméthylamino)-5-oxytétracycline, la 4-de(diméthylamino)-7-chlorotétracycline, la 6-deoxydeméthyl-4-dediméthylamino-tétracycline, et la 6-ä-déoxy-5-hydroxy-4-dediméthylamino-tétracycline.
4. Une composition selon la revendication 3 où la tétracycline est la 6-ä-benzylthiométhylentétracycline, l'analogue 2-nitrilo de la tétracycline, l'amide mono-N-alcoylée de tétracycline, la 6-fluoro-6-deméthyltétracycline, ou la 11-ä-chlorotétracycline.
5. Une composition selon la revendication 1 où l'agent non-stéroïde anti-inflammatoire est sélectionné parmi des salicylates, des acides acétiques, des acides propioniques, des fenamates, des pyrazoles, et des oxicams.
6. Une composition selon la revendication 5 où le salicylate est sélectionné entre l'acide acétylsalicylique et le diflunisal, l'acide acétique est sélectionné entre l'indométhacine, le sulindac, la tolméthine, le diclofenac et l'étodolac, l'acide propionique est sélectionné entre le flurbiprophène, le naproxène, le kétoprophène, et l'ibuprophène, l'oxicam est sélectionné entre le piroxicam et l'isoxicam, et le fenamate est sélectionné entre le meclofenamate et l'acide flufenamique.
7. L'utilisation de (a) une quantité d'une tétracycline qui est effectivement anticollagénase mais qui n'est pas effectivement antimicrobienne, et (b) une quantité d'agent non-stéroïde anti-inflammatoire qui, lorsqu'elle est combinée à la quantité effectivement anticollagénase de tétracycline, produit une réduction notable de la déperdition osseuse, pour la préparation d'un produit pharmaceutique, qui contient (a) et (b) en préparation combinée en vue d'une utilisation simultanée, séparée ou séquentielle dans le traitement d

mammifères souffrant de polyarthrite rhumatoïde et d'autres affections destructrices des tissus associées à une activité excessive de métalloprotéinases.

5

10

15

20

25

30

35

40

45

50

55

FIG. 1

